Listing of the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (currently amended) A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model;

b) selecting an initial set of candidate models by selecting one feature from each set of mutually exclusive features by a uniform random process for each candidate model;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is -2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if not estimation correlations are > 0.95 and 1 if at least one is > 0.95 and

correlation penalty is the penalty for a correlation of > 0.95;

e) searching said models using the objective ~~functions~~ function and a method selected from the group consisting of: full grid search, simulated annealing, integer programming, scatter search/path relinking, neural networks, tabu search and genetic algorithm to select the next set of models;

f) repeating steps c) to e) with the selected method of searching and next set of models until no further improvement in the lowest value of overall functions of models is achieved;

g) selecting the model with lowest value of the objective function as the optimal or near optimal model.

2. (canceled)

3. (canceled)

4. (currently amended) The method of claim 1, wherein ~~the~~ NONMEM/NMTRAN control files are generated for each model selected in step b) or step e) by substituting text associated with each selected feature into a control file template;

~~the~~ NONMEM/NMTRAN is run using ~~the~~ said control files; and

the computed goodness of fit (fitness) is input to an overall objective function generator to compute the overall objective function in step d[[)]].

5. (currently amended) The method of claim 1, wherein the overall function is computed by combining the -2 * log likelihood value with a penalty for each parameter estimated, a penalty for each element of the interindividual variance matrix estimated, a penalty for each element of the intraindividual variance matrix estimated, a penalty imposed if the minimization does not conclude successfully, a penalty if the

standard errors of the parameter estimates cannot be obtained, a penalty if the correlation matrix of the estimates has any element > 0.95, and a "niche" penalty for being similar to other models in the population (within a "niche radius" of other models).

6. (currently amended) A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model;

b) selecting an initial set of candidate models by selecting one feature from each set of mutually exclusive features by a uniform random process for each candidate model and representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is -2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful,

correlation is 0 if not estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation of > 0.95;

e) optionally, scaling the overall objective function of each model to be between ~~and~~ an upper limit R and a lower limit S wherein the ratio of R to S is between 2:1 and 100:1;

f) providing a number y of models to be in a subsequent generation;

g) selecting with replacement y number of parents of the said subsequent generation from the current generation, wherein the probability of selection of a model in the current generation is proportional to said fitness or optionally to said scaled fitness;

h) associating said parents into m groups comprising p parents where p is an integer greater than 1;

i) optionally, selecting some fraction of the m groups of parents to undergo at least one cross over;

j) optionally, crossing over said selected fraction at a random location on said bit string to create two new individuals for said subsequent generation;

k) assigning bit strings in current generation that are not selected for cross over to said subsequent generation;

l) optionally, randomly mutating bits of said subsequent generation bit strings wherein said mutation comprises changing a bit value 0 to a bit value of 1 or changing a bit value of 1 to a bit value of 0; and

m) repeating the steps of c through l until further decrease in the lowest value of the overall objective function (improvement in maximum fitness) no longer occurs.

7. (canceled)

8. (canceled)

9. (canceled)

10. (original) The method of claim 6 wherein the ratio of R to S is between 10:1 and 50:1.

11. (original) The method of claim 6, wherein the number of models in the subsequent generation is equal to the number of models in the current generation.

12. (original) The method of claim 6 wherein $p = 2$.

13. (original) The method of claim 6 wherein said fraction to undergo at least one cross over is selected randomly.

14. (original) The method of claim 6 wherein said fraction to undergo at least one cross over is between 0.4 to 1.0

15. (previously presented) The method of claim 6 wherein said models represent pharmacokinetic models and/or pharmacodynamic models.

16. (original) The method of claim 15 wherein said sets of mutually exclusive features comprise one or more members of the group consisting of: the number of pharmacokinetic compartments, the presence of non-linear elimination, the presence of non-linear absorption, the presence of interindividual variability on each parameter, the function describing the interindividual variability of each parameter, the function describing the residual variability, the structure of the interindividual covariance matrix, emax pharmacodynamic model, linear pharmacodynamic model, types 1 through 4 indirect response pharmacodynamic model, the presence of an effect compartment, the relationship between drug elimination and age, the relationship

between drug elimination and renal function, the relationship between drug elimination and liver function, the relationship between drug elimination and gender, the relationship between drug elimination and weight, the relationship between drug volume of distribution and age, the relationship between drug volume of distribution and gender, the relationship between drug volume of distribution and weight, the relationship between drug volume of distribution and cardiac function, the relationship between drug volume of distribution and renal function, the relationship between drug volume of distribution and liver function, the relationship between drug bioavailability and age, the relationship between drug bioavailability and gender, the relationship between drug bioavailability and weight, the relationship between drug bioavailability and liver function, the relationship between drug bioavailability and renal function.

17. (currently amended) A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model;

b) selecting an initial set of candidate models by selecting one feature from each set of mutually exclusive features by a uniform random process for each candidate model and representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is -2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if not estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation of > 0.95;

e) searching the candidate search space using simulated annealing, wherein simulated annealing comprises the steps of:

i) randomly selecting one model from the candidate set of models;

ii) selecting an initial value for temperature (T) wherein T represents the tolerance of a minimization process for retaining a model that results in a higher energy; and T is defined as a change in value of the overall objective function;

iii) assessing the energy of the initial model, wherein energy is defined as the value of the overall objective function;

iv) randomly changing the model to generate a subsequent model;

v) assessing the energy of the subsequent model using the methods of steps c) and d) above;

vi) retaining the subsequent model as the current model if the energy is lower than the current model;

vii) if the energy of the subsequent model is higher than the energy of the current model, computing the probability of retaining it as:

$$e^{\frac{\Delta E}{KT}}$$

where T is the temperature, ΔE is the change in energy (current model energy – subsequent model energy), and k is ~~Boatman's~~ Boltzman's constant, or

Otherwise, rejecting the subsequent model;

viii) reducing the value of T;

ix) randomly selecting one model from the candidate set of models; and

x) repeating the steps of iv through ix until further reduction in energy (overall objective function) no longer occurs.

18. (previously presented) The method of claim 17 wherein said sets of mutually exclusive features comprise one or more members of the group consisting of: the number of pharmacokinetic compartments, the presence of non-linear elimination, the presence of non-linear absorption, the presence of interindividual variability on each parameter, the function describing the interindividual variability of each parameter, the function describing the residual variability, the structure of the interindividual covariance matrix, emax pharmacodynamic model, linear pharmacodynamic model, types 1 through 4 indirect response pharmacodynamic model, the presence of an effect compartment, the relationship between drug elimination and age, the relationship between drug elimination and renal function, the relationship between drug elimination and liver function, the relationship between drug elimination and gender, the relationship between drug elimination and weight, the relationship between drug volume of distribution and age, the relationship between drug volume of distribution and gender, the relationship between drug volume of distribution and weight, the relationship between drug volume of distribution and cardiac function, the relationship between drug volume of distribution and renal function, the relationship between drug volume of distribution and liver function, the

relationship between drug bioavailability and age, the relationship between drug bioavailability and gender, the relationship between drug bioavailability and weight, the relationship between drug bioavailability and liver function, the relationship between drug bioavailability and renal function.

19. (canceled)

20. (canceled)

21. (currently amended) A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and

b) selecting an initial set of candidate models by selecting one feature from each set of mutually exclusive features by a uniform random process for each candidate model and representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is -2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the

penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if not estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation of > 0.95;

e) initializing the search with a call to ~~OCL setup~~ OCLSetup in the OptQuest callable library and ~~initialize~~ initializing a population of models with a call to OCLInitPop;

f) initializing each search dimension with a call to ~~OCLdefinevar~~ OCLDefineVar in the OptQuest callable library;

g) selecting an initial model from the candidate search space using scatter search/path relinking and tabu search as implemented in the OptQuest Callable library from OptTek systems by calling the function ~~Octretsolution~~ OCLGetSolution;

h) searching the candidate search space using Scatter search/path ~~relinlking/Tabu~~ relinking/Tabu search using the OptQuest Callable library wherein Scatter search/path relinking/Tabu search comprises the steps of:

i) evaluating the overall objective function of the current model;

ii) adding the value of the overall objective function of the current model to the OptQuest Callable library database with a call to the function ~~OCL putsolution~~ OCLPutSolution;

iii) finding the overall objective function of the best model thus far evaluated with a call to the function OCLGetBest in the OptQuest Callable Library;

iv) getting the subsequent model with a call to the function OCLGetSolution; and

v) repeating steps i-iv until either the required number of evaluations or convergence is seen; and

i) deleting current problem from memory with a call to OCLGoodBye.

22. (original) The method of claim 21 wherein said sets of mutually exclusive features comprise one or more members of the group consisting of: the number of pharmacokinetic compartments, the presence of non-linear elimination, the presence of non-linear absorption, the presence of interindividual variability on each parameter, the function describing the interindividual variability of each parameter, the function describing the residual variability, the structure of the interindividual covariance matrix, emax pharmacodynamic model, linear pharmacodynamic model, types 1 through 4 indirect response pharmacodynamic model, the presence of an effect compartment, the relationship between drug elimination and age, the relationship between drug elimination and renal function, the relationship between drug elimination and liver function, the relationship between drug elimination and gender, the relationship between drug elimination and weight, the relationship between drug volume of distribution and age, the relationship between drug volume of distribution and gender, the relationship between drug volume of distribution and weight, the relationship between drug volume of distribution and cardiac function, the relationship between drug volume of distribution and renal function, the relationship between drug volume of distribution and liver function, the relationship between drug bioavailability and age, the relationship between drug bioavailability and gender, the relationship between drug bioavailability and weight, the relationship between drug bioavailability and liver function, the relationship between drug bioavailability and renal function.

23. (currently amended) A computer program product comprising computer usable storage medium having computer executable instructions which when executed on a computer perform a process for selecting a near optimal or optimal mathematical model from a set of candidate models, the process comprising:

a) defining a candidate model search space having n dimensions, wherein n is a

positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model;

b) selecting an initial set of candidate models by selecting one feature from each set of mutually exclusive features by a uniform random process for each candidate model;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is -2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if not estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation of > 0.95;

e) searching said models using the objective ~~functions~~ function and a method selected from the group consisting of: full grid search, simulated annealing, integer programming, scatter search/path relinking, neural networks, tabu search and genetic algorithm to select the next set of models;

f) repeating steps c) to e) with the selected method of searching and next set of models until no further improvement in the lowest value of overall functions of models is achieved;

g) selecting the model with lowest value of the objective function as the optimal or near optimal model.

24. (canceled)

25. (canceled)

26. (currently amended) A computer program product comprising computer usable storage medium having computer executable instructions which when executed on a computer perform a process for selecting a near optimal or optimal mathematical model from a set of candidate models, the process comprising:

a) defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model;

b) selecting an initial set of candidate models by selecting one feature from each set of mutually exclusive features by a uniform random process for each candidate model and representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is -2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model,[[),]] theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the

minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if not estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation of > 0.95;

e) optionally, scaling the overall objective function of each model to be between ~~and~~ an upper limit R and a lower limit S wherein the ratio of R to S is between 2:1 and 100:1;

f) providing a number y of models to be in a subsequent generation;

g) selecting with replacement y number of parents of the said subsequent generation from the current generation, wherein the probability of selection of a model in the current generation is proportional to said fitness or optionally to said scaled fitness;

h) associating said parents into m groups comprising p parents where p is an integer greater than 1;

i) optionally, selecting some fraction of the m groups of parents to undergo at least one cross over;

j) optionally, crossing over said selected fraction at a random location on said bit string to create two new individuals for said subsequent generation;

k) assigning bit strings in current generation that are not selected for cross over to said subsequent generation;

l) optionally, randomly mutatating bits of said subsequent generation bit strings wherein said mutation comprises changing a bit value 0 to a bit value of 1 or changing a bit value of 1 to a bit value of 0; and

m) repeating the steps of c through l until further decrease in the lowest value of the overall objective function (improvement in maximum fitness) no longer occurs.

27. (canceled)

28. (canceled)